a2 cont.

(b) identifying a compound that inhibits or reduces pathogenicity of [the] said same pathogen in said [eukaryotic host organism] nematode and said plant.

a3

26. (Amended) The method of claim [25] 22, wherein said nematode is *Caenorhabditis elegans*.

a4

28. (Amended) The method of claim [27] 22, wherein said plant is *Arabidopsis*.

REMARKS

Summary of Office Action

Claims 1-30 are pending in the application. Claims 1-14 and 20-30 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-25 of copending Application No. 08/852,927. Claims 1-30 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 1-30 stand rejected under 35 U.S.C. § 112, second paragraph. And claims 1-30 stand rejected under 35 U.S.C. § 103(a). Each of these rejections is addressed as follows.

Amendments

The specification has been amended to correct the typographical errors noted in the Office Action. In addition, claims 1 and 22 have been amended to clarify the

language of these claims. Support for these amendments may be found, for example, at page 60, lines 25-26, and at page 62, line 12. Claim 22 was also amended to include the limitations of dependent claims 25 and 27. No new matter has been added by these amendments.

Double Patenting

Claims 1-14 and 20-30 stand rejected, under 35 U.S.C. § 101, as claiming the same invention as that of co-pending Application No. 08/852, 927. Because Application No. 08/852,927 has been abandoned, this rejection is moot.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-30 stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action, at page 4, asserts:

> [T]he claims do not restrict the identification of a compound by testing said compound, but the scope of the claims encompass such identification by testing any other compounds. The claims do not restrict the testing to the same pathogen, but the "a single" pathogen to which the at least two different eukaryotic organisms are exposed may be different from the pathogen of the preamble of claim 1 [emphasis original].

In view of the present amendment to claim 1, which requires that the claimed method includes the step of detecting inhibition or reduction of pathogenicity of the pathogen (i.e., the pathogen recited in the preamble) as an indication that the candidate

compound inhibits or reduces pathogenicity of the pathogen, this rejection may be withdrawn.

Claims 1-30 also stand rejected, under § 112, first paragraph, based on the assertion that applicants' specification is not commensurate in scope with the present claims. The rejection turns on the contention that:

> The scope of the instant [specification] encompasses identification of a compound capable of inhibiting Herpes simplex virus in humans by "exposing" lettuce and celery to the virus in the presence of a candidate compound. However, the specification does not teach that Herpes simplex virus infects/multiplies in such plants. Thus, the specification only teaches the use of pathogens and eukaryotic organisms which have been shown to exhibit such a host/infection relationship.

Applicants submit that the current claims are clearly enabled for identifying any number of compounds that inhibit or reduce the pathogenicity of virtually any pathogen that infects at least two different eukaryotic organisms. Applicants first point out that their specification, for example, at page 63 (lines 18-20), makes clear that the methods of the invention are useful for:

> screening compounds having an effect on a variety of pathogens including, but not limited to, bacteria, viruses, fungi, annelids, nematodes, platyhelminthes, and protozoans.

In addition, applicants point out that the specification, for example, at pages 23-24, teaches screening systems for identifying common virulence genes of a pathogen that are involved in pathogenicity of diverse hosts such as nematodes, plants, and yeast or other fungi, as well as fish, flies, and mice. Moreover, applicants' specification, for example, at

pages 58-65, provides straightforward methods for identifying therapeutic compounds (e.g., anti-pathogenicity pharmaceuticals) which target common virulence genes of pathogens that infect at least two different eukaryotic organisms, for example, animals or plants. Based on this description, applicants' specification cannot reasonably be construed as limited to teaching "the use of pathogens and eukaryotic organisms which have been shown to exhibit such a host/infection relationship." Applicants respectfully request that the Office reconsider and withdraw the rejection under § 112, first paragraph, and find that applicants' specification enables the invention as presently claimed.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-30 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on several grounds, which are addressed as follows.

Claim 1 stands rejected in reciting the phrase "said pathogen" on the ground that it is unclear which "said pathogen" is referred to in the claim — the pathogen of the preamble or the "a single pathogen." This rejection has been met by amending the claim to refer specifically to the pathogen of the preamble, that is, "the same pathogen." Claim 22 which includes this terminology has been amended similarly.

Claim 1, without explanation, was also deemed indefinite in reciting the term "exposing." Applicants assert that this term is definite since "exposing" connotes in this context that the different eukaryotic organisms are brought into contact with the single

pathogen. This rejection may be withdrawn.

Claim 1 was also deemed indefinite in reciting the phrase "at least two different" eukaryotic organisms based on the assertion it is unclear whether the eukaryotic organisms are different from the eukaryotic organism of the preamble or from each other. This rejection has been met by the present amendment to the preamble of claim 1 which specifies that the methods are for determining whether a compound "inhibits or reduces pathogenicity of the same pathogen in at least two different eukaryotic organisms." This rejection may be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1-30 stand rejected, under 35 U.S.C. § 103(a), as being unpatentable over Elrod et al. (*J. Bacteriol.* 46:633-645, 1942; "Elrod") or Schroth et al. (*Pseudomonas aeruginosa: Ecological Aspects and Patient Colonization*, pp. 1-29, 1977; "Schroth") in view of Kominos et al. (*Appl. Microbiol.* 24(4): 567-570, 1972; "Kominos") and further in view of Geels (*J. Appl. Bacteriol.* 79: 38-42, 1995; "Geels") and Conrad et al. (*Rev. Inf. Dis.* 13: S364-369, 1991; "Conrad").

The claims, as amended, cover methods for identifying a compound that inhibits or reduces the pathogenicity of the same pathogen in at least two different eukaryotic organisms (claim 1), as well as methods for identifying a compound that inhibits or reduces the pathogenicity of the same pathogen in a nematode and plant (claim 22).

Because none of the cited reference combinations teaches or suggests applicants' invention, this rejection is respectfully traversed.

Looking first to Elrod, applicants maintain that this reference does not teach or suggest that compounds may be identified that inhibit or reduce the pathogenicity of a single pathogen using methods involving at least two different eukaryotic organisms, let alone identifying compounds that inhibit or reduce the pathogenicity of such a pathogen using a combination of nematode and plant assay systems. Instead the opposite teaching is found in the Elrod reference. Although Elrod recognizes that the pathogen, *Pseudomonas aeruginosa,* is capable of infecting both humans and plants, Elrod, unlike applicants, concluded that such dual pathogenicity resulted, not from the existence of common virulence factors found in the bacterium, but rather from the existence of different virulence factors, and possibly even from the existence of different strains of the same bacterium, each being responsible for causing infection in either a plant or a human. Evidence for this assertion is found, for example, at page 642 of the Elrod teaching, where the reference clearly states (emphasis added):

> It appears likely that the **phytotoxic [plant pathogenic] factors** of the organism [P. aeruginosa] **are not the same as the toxin substances that induce animal disease**. This was emphasized by the action of **rough variants** which, though not fatal to animals, retained their pathogenicity for plants.

Indeed, this passage indicates that Elrod interpreted his results as teaching (1) that factors contributing to pathogenicity in plants and humans are "not the same," and (2) that

there may well be different strains of the bacterium, i.e., "rough variants," which are pathogenic for one organism but not the other. Nowhere does Elrod suggest applicants' discoveries that the same strain can infect plants and animals, that common pathogenic virulence factors exist, or that compounds for use in higher organisms may be identified and evaluated in simple host systems, as described in applicants' specification and as claimed in the present case.

Moreover, with respect to the Elrod reference, applicants emphasize the fact that Elrod plainly teaches away from applicants' discovery of common virulence factors, suggesting instead that pathogenicity in different organisms requires different factors. The Office must, under the case law, "consider such evidence in connection with the determination of obviousness." *In re Sernaker*, 702 F.2d 989, 996, 217 U.S.P.Q. 1, 7 (Fed. Cir. 1983). It is therefore incumbent upon the Office to address the Elrod teaching in view of the above passage which discredits any interpretation of this reference as teaching applicants' discovery.

Turning to the other primary reference, Schroth, the Office Action asserts that this reference teaches "that *Pseudomonas aeruginosa* infects patients in hospitals as well as agricultural plants." While applicants do not specifically disagree with this characterization of the Schroth reference, they point out that this reference does not teach that the same strain of *Pseudomonas* is responsible for both infections. Indeed, in view of Elrod, one skilled in the art would be led to believe that these infections were caused by

different strains, one specific for human patients and the other specific for agricultural plants. Moreover, like the Elrod reference, Schroth entirely fails to recognize that dual pathogenicity results from the existence of common virulence factors, and absent this recognition this reference is incapable of providing a logical basis for suggesting that effective inhibitory compounds for treating or preventing a pathogen infection in one eukaryotic organism might be identified by screening for those compounds in an entirely different eukaryotic organism.

With respect to Kominos, the Office Action contends that this reference teaches "that vegetables are an important source and vehicle by which *P. aeruginosa* colonizes the intestinal tract of patients." As an initial matter, applicants point out that this reference never teaches or suggests that a single pathogen possesses common virulence factors that render it pathogenic on multiple host organisms. Moreover, the finding that certain vegetables serve as a reservoir for *P. aeruginosa* provides no reasonable basis for concluding that screening methods might be developed to identify compounds that inhibit or reduce the pathogenicity of such a pathogen using methods involving two different organisms such as plants and animals. Kominos, even when combined with Elrod and Schroth, does not teach or suggest applicants' discovery that common pathogenic virulence factors are involved in the infection of widely divergent animal species as well as plants, much less that nematodes and plants may be used together to identify compounds that inhibit or reduce the pathogenicity of a pathogen.

With respect to Conrad, the Office Action states that this reference teaches "human clinical models to identify a compound (aztreonam) which is efficacious for treatment of a pathogen (*P. aeruginosa*)." Conrad, however, does not suggest applicants' invention, nor does it provide any motivation for its combination with the primary references. Conrad is singularly focused on determining the efficacy of one particular compound to treat *P. aeruginosa* skeletal infections in humans. Conrad never even mentions that screening systems apart from the described skeletal system might be used to evaluate the efficacy of aztreonam. Morever, Conrad, like all of the cited references, fails to recognize the existence of common pathogenic virulence factors that facilitate the claimed screening methods in multiple eukaryotic organisms designed to identify therapeutic agents useful for pathogen inhibition or reduction of pathogenicity.

Finally, with respect to Geels, the Office Action states that this reference teaches a "plant model to identify a compound (kasugamycin) which is efficacious for treatment of a pathogen (*P. tolaasii*)." The Office Action, however, attributes to Geels teachings not found in the reference. As the title of the reference indicates, Geels teaches "*Pseudomonas tolaasii* control by kasugamycin in cultivated mushrooms (*Agaricus bisporus*)." Because mushrooms are fungi and not plants, Geels does not teach any plant model to identify compounds that are efficacious for treating a plant pathogen, and certainly does not teach any method of using two different eukaryotic organisms to identify compounds that inhibit or reduce the pathogenicity of the same pathogen.

In sum, no evidence made of record in this case indicates that, at the time of applicants' invention, one skilled in the art would have recognized that evolutionarily diverse organisms, such as plants and animals, might be used together to develop assays for screening candidate compounds for anti-pathogenic activity. The obviousness analysis articulated in the Office Action is limited entirely to a discussion focusing on the assertion that "*P. aeruginosa* is a pathogen frequently involved in disease in both plants and animals." No analysis of the cited publications is presented that explains what specific understanding, theory, or technical principle found in these references would have suggested a combination leading to applicants' claimed screening methods. Applicants' technical breakthrough demonstrating the existence of common virulence factors that are used by pathogens to infect multiple hosts is nowhere taught or suggested by the cited publications. Instead, the present rejection hinges essentially on some observations about *Pseudomonas* pathogenicity — one of which is over fifty years old — that provide no reasonable scientific basis for developing applicants' claimed methods.

The combination of Elrod, Schroth, Kominos, Geels, and Conrad simply does not teach or suggest the presently claimed invention. The § 103(a) rejection may be withdrawn.

Conclusion

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including July 21, 1999. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 7/21/99

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